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Variant: NM_000277.3(PAH):c.1252A>C (p.Thr418Pro)

Version: 1.0

CA229418

102580 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 8328fe09-187d-4840-9cd3-5e9160964b68
Approved on: 2020/6/8
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HGVS expressions

NM_000277.3:c.1252A>C
NM_000277.3(PAH):c.1252A>C (p.Thr418Pro)
NC_000012.12:g.102840463T>G
CM000674.2:g.102840463T>G
NC_000012.11:g.103234241T>G
CM000674.1:g.103234241T>G
NC_000012.10:g.101758371T>G
NG_008690.1:g.82140A>C
NG_008690.2:g.122948A>C
ENST00000553106.6:c.1252A>C
ENST00000307000.7:c.1237A>C
ENST00000551114.2:n.914A>C
ENST00000553106.5:c.1252A>C
ENST00000635477.1:c.356A>C
ENST00000635528.1:n.767A>C
NM_000277.1:c.1252A>C
NM_000277.2:c.1252A>C
NM_001354304.1:c.1252A>C
NM_001354304.2:c.1252A>C

Pathogenic

Met criteria codes 4

PM3_Very Strong | PM2 | PP4_Moderate | PP3

Not Met criteria codes 2

BS3 | PS3

Evidence Links 3

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1252A>C (p.Thr418Pro) variant in PAH has been reported in multiple individuals with mild and classic PKU (BH4 deficiency excluded). (PMID: 26503515). This variant has an extremely low allele frequency (MAF=0.00003) in gnomAD. It was detected in trans with multiple pathogenic variants: p.Arg243Gln, p.Arg408Gln, p.Arg176*, EX6-96A□G, p.Tyr356*, p.Arg111* (PMID: 28982351). Computational prediction tools and conservation analysis support a deleterious effect. In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM3_very-strong, PM2, PP4_Moderate, PP3.

Met criteria codes

PM3_Very Strong	✔	p.Arg243Gln (P 11 submitters), p.Arg408Gln (P 7 submitters), p.Arg176* (P 9 submitters), EX6-96A□G (P 6 submitters), p.Tyr356*(P), p.Arg111* (P 6 submitters); variable sites in patient genes were aligned with the corresponding sites from the respective parents. PMID: 28982351
PM2	✔	absent in 1000G and Exac. MAF=0.00003 in gnomAD.
PP4_Moderate	✔	Seen in multiple individuals with PKU. Biochemical testing data, including plasma phenylalanine (Phe) levels, dihydropteridine reductase activity, urinary biopterin and neopterin ratio, and tetrahydrobiopterin loading, were collected. PMID: 26503515 Seen in a patient with Classic PKU (Phe < 1200 lmol/L)) in trans with EX6-96A>G PubMed:16256386 Seen in multiple individuals with PKU, these patients were diagnosed at birth either through a neonatal screening program or based on clinical presentation. Biochemical testing data, including plasma phenylalanine (Phe) levels, dihydropteridine reductase activity, urinary biopterin and neopterin ratio, and tetrahydrobiopterin loading, were collected. PubMed:26503515
PP3	✔	Multiple lines of evidence (MutationTaster, SIFT, Polyphen) support deleterious effect.

Not Met criteria codes

BS3	✖	In vivo studies show a 105 and 106 % PAH enzymatic activity. In vivo studies show a 105 and 106 % PAH enzymatic activity. Site-directed mutagenesis and in vitro expression analysis were performed as previously described (Svensson et al., 1992). Immunoreactivity 79,95 % wt. RNA level 105, ND. cos cells transfected with PAH cDNA. PubMed:8019568
PS3	✖	In vivo studies show a 105 and 106 % PAH enzymatic activity. In vivo studies show a 105 and 106 % PAH enzymatic activity. Site-directed mutagenesis and in vitro expression analysis were performed as previously described (Svensson et al., 1992). Immunoreactivity 79,95 % wt. RNA level 105, ND. cos cells transfected with PAH cDNA. PubMed:8019568

Curation History

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